REMARKS

Upon entry of the amendment, claims 37, 43 and 101-105 will be pending in the application. Claims 38-42 and 44-100 are cancelled with the present amendment and new claims 101-105 added. Claims 37 and 43 are amended. Support for the amendments to claim 37 appears in, e.g., now cancelled claims 38, 42 and 50 and in the specification at page 7, lines 11-20, and at page 24, line 24 – page 25, line 19. New claims 101-105 are supported in the specification at, e.g., the specification at page 6, lines 23-25, page 9; lines 33-38; page 23, lines 15-20 and lines 32-37 and page 27, lines 33-38.

No new matter is added by these amendments. The cancellation of claimed subject matter of does not constitute an admission by Applicants that the subject matter no longer claimed is not patentable. Applicants reserve the right to pursue all cancelled subject matter in a continuing application or applications.

Applicants enclose an Information Disclosure Statement and a certified copy of priority application PCT/IL99/00444 filed August 17, 1999.

Rejections under 35 U.S.C. 112, First Paragraph

Claims 37-43 are rejected for overbreadth. Claims 38-42 are cancelled. The rejection is traversed to the extent it is applied to the pending claims as amended and added herein.

Independent claim 37, from which claims 101-103 depend, has been amended so that it is drawn to a method of expanding a population of hematopoietic cells in an individual in need of hematopoietic cell expansion by administering to a patient in need thereof an effective amount of

a transition metal chelator having affinity for copper. The claim additionally requires that the chelator inhibits differentiation of the hematopoietic cells.

Applicants respectfully submit that the full breadth of the invention now claimed can be practiced using the knowledge available to one of ordinary skill in the art when coupled with the teachings of the specification. Suitable reference concentrations for the recited transition metal chelator is provided at page 25, lines 30-34. Suitable chelators are disclosed at page 25, line 35 to page 26, line 11. Formulations and dosage regimens for administering the chelators are described at, e.g., page 24, line 31 to page 25, line 19.

The claimed in vivo methods are further supported by the teachings and examples provided in the specification relating to the in vitro effects of transition metal chelators on hematopoietic cells. Applicants note that the Examiner acknowledges that the specification enables claims drawn to the expansion $CD34^+$ cell populations ex-vivo while inhibiting differentiation but contends that the specification is not enabled for expansion of any cells in vivo while inhibiting differentiation (*See*, Office Action at pages 2-3). However, the specification teaches that transition metal chelators are effective in enhancing expansion and inhibiting differentiation of hematopoietic cell types in addition to those that are CD34+ selected. Pages 37, line 10 to page 38, line 10, and Table 2 of Example 1 of the specification teaches that transition metal chelators stimulate expansion while inhibiting differentiation of murine erythroleukemia cell cultures as well as undifferentiated CD34+ cells. Other examples of growth induction and inhibition of cell differentiation by transition metal chelators in diverse cell populations at various stages of differentiation are also taught in the specification (*See*, for example, Table 2- Effect of TEPA on murine erythroleukemia cells; Figure 5, effect of TEPA on erythroid precursors form peripheral blood mononucleocytes; Example 4, Table 4, Effect of

TEPA on embryonal stem cells; and page 48, Example 4- Effect of TEPA on hepatocyte growth and differentiation).

The attached Declaration of Eitan Fibach[1] ("the Fibach Declaration") provides additional evidence that non-CD34+ selected cells proliferate in vitro without differentiating when exposed to a transition metal chelator. The Fibach Declaration examines the effects of transition metal chelators on AC133+-selected cells. AC133 cells have high self-renewal capability, maintain early hematopoietic stem/progenitor cell (HSPC) characteristics, and show superior survival in culture, as compared to CD34+ cells.

The Fibach Declaration demonstrates that following a three week large-scale clinical grade expansion, the yield of cord blood-derived early progenitor cells (TNC, CFUc, CD34+ cells and CD34+CD38- cells) in high affinity transition metal chelator-supplemented (5 μM TEPA) culture initiated with AC133+ cells was statistically similar with that initiated with a same number of CD34+ cells. In addition, similar proportions of cells expressing myeloid, lymphoid and megakaryocytic phenotype were found in cultures initiated either with CD34+ or AC133+ cells.

Supporting these teachings of the specification is the highly developed art of administering transition metal chelators in vivo. Transition metal chelators have been used to treat, e.g., heavy metal poisoning, (*See*, Vilensky et al., Ann Emerg Med 41:378-383, 2003, attached as Exhibit A); Wilson's disease (*See*, Hottinger et al., Eur J Neurosci 9:1548-1551, 1997, attached as Exhibit B); and prion-associated disease (*See*, Sigurdsson et al., J Biol Chem 278:46199-46202, 2003, attached as Exhibit C).

[1] The Declaration has been submitted for a response in copending application USSN 09/463,320.

Applicants note the Examiner's statement that the present invention must be considered unpredictable since the mechanism of the effects of copper are as yet unknown (*See*, Office Action at page 3). Applicants respectfully submit that this is an improper basis by which to evaluate the enablement of the claimed invention. The Federal Circuit has stated in In re Cortright, 165 F.3d 1353 (1999):

> It is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); see also Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). Furthermore, statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained.

Thus, while understanding of the effects of copper on the process of differentiation will undoubtedly be of great value, such understanding is not necessary for enabling the claimed invention.

The Examiner additionally states that in vivo administration of transition metal chelators is toxic and a potential health hazard (*See*, Office Action at pages 3-4). This is an improper enablement rejection under MPEP § 2107.03, which states that it is improper to request evidence of safety in the treatment in humans or regarding the degree of effectiveness of treatment in humans:

> "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)).
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> Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of

safety in the treatment of humans, or regarding the degree of effectiveness. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

Moreover, as discussed above, transition metal chelators are used in vivo for treating other conditions (*See*, Dubois et al., J Pediatr Gastroenterol Nutr 10:77-81, 1990 (attached as Exhibit D); Shimizu et al., Pediatr Int 41: 419-422, 1999 (Exhibit E); Suda et al., No To Hattatsu 25: 429-434, 1993; and abstracts for TOXLINE, HAZARD, and Material Safety Data Sheet for TETA and TEPA, abstracts attached as Exhibits F-J), Thus, the literature provides clear direction for the administration of copper chelators in vivo and the information in the Merck Manual and Safety Sheet data do not preclude the in-vivo use of TETA, TEPA or similar drugs for expanding hematopoietic stem and progenitor cell populations.

In view of the foregoing comments, reconsideration and withdrawal of the rejection for overbreadth is respectfully requested.

Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for a three-month extension of time and for extending the deadline for responding to the Office Action and fee accompanies this response. The Commissioner is authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 24024-501CON2B.

Respectfully submitted,

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